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# VOSSIUS & PARTNER

Patentanwälte

Vossius & Partner POB 860767 81634 München Germany

To the
European Patent Office
Munich

PATENTANWÄLTE
EUROPEAN PATENT ATTORNEYS
EUROPEAN TRADEMARK ATTORNEYS
Dr. VOLKER VOSSIUS, Dipl.-Chem.
(bis 1992; danach in anderer Kanzlei)
Dr. PAUL TAUCHNER, Dipl.-Chem.
Dr. DIETER HEUNEMANN, Dipl.-Phys.
Dr. PETER A. RAUH, Dipl.-Chem.
Dr. GERHARD HERMANN, Dipl.-Phys.
JOSEF SCHMIDT, Dipl.-Ing.
Dr. HANS-RAINER JAENICHEN, Dipl.-Biol.
Dr. ALEXA VON UEXKÜLL, M.Sc.
Dr. RUDOLF WEINBERGER, Dipl.-Chem.
Dr. WOLFGANG BUBLAK, Dipl.-Chem.
AXEL STELLBRINK, Dipl.-Ing.
Dr. JOACHIM WACHENFELD, (Biol.)
Dr. FRIEDERIKE STOLZENBURG, Dipl.-Biol.
RAINER VIKTOR, Dipl.-Ing.
EUROPEAN PATENT ATTORNEYS
Dr. RENATE BARTH, Dipl.-Chem.
Dr. URSULA ENGLBRECHT, Dipl.-Chem.
Dr. PETER EINMAYR, Dipl.-Chem.
RECHTSANWÄLTE
HELGA TREMMEL
BARBARA GUGGENMOS, Dipl.-Chem.
DR. THURE SCHUBERT
SIMONE SCHÄFER

SIEBERTSTRASSE 4
81675 MÜNCHEN
GERMANY
TEL.: +49-89-41 30 40
FAX: +49-89-41 30 41 11 (G3/G4)
+49-89-41 30 44 00 (G3)
(Marken - Trademarks)
E-MAIL: info@vossiusandpartner.com
HOMEPAGE: www.vossiusandpartner.com



EP 0 682 040 B1
(EP 95 10 5609.2)
Protein Design Labs, Inc.
HLBB File: GFOP 00 828 (Lit. No. 376)
Vossius & Partner Ref.: B 1060 EP/I

July 13, 2001
Jae/PST/elh

Please be informed that our firm Vossius & Partner will act henceforth as co-representative of the Patentee in this case. Enclosed please find a corresponding authorization by the Patentee. However, please note that Hepworth, Lawrence, Bryer & Bizley and Mr. Richard Bizley specifically remain the address for service in this case. It is therefore respectfully requested that the European Patent Office should continue to direct all formal correspondence and copy correspondence to Mr. Richard Bizley.

Reference is made to Patentee's petition dated May 11, 2001 and to the Communication of Notices of Opposition dated September 4, 2000.

These are Patentee's observations pursuant to Article 101(2) and Rule 57(1) EPC to the oppositions against PDL's patent EP-B1 0 682 040 (hereinafter referred to as the "contested Patent") filed by

I. Dr. Charles T. Harding
II. Boehringer Ingelheim GmbH
III. MedImmune Inc.
IV. Schering Corporation
V. Celltech Chiroscience Limited
VI. Xoma (US) LLC
VII. Novartis AG
VIII. IDEC Pharmaceuticals Corporation

In the following, the parties are referred to as "Opponent I", "Opponent II", etc... .

In order to simplify reference to any documents, we enclose 9 copies of a consolidated list of all documents cited by the Opponents and by us in these observations (Annex I). Each of these documents is now given a consecutive number to aid reference by the Opposition Division.

## 1. INTRODUCTION

The invention claimed in the patent relates generally to the combination of recombinant DNA and monoclonal antibody technologies for the production of non-immunogenic antibodies and their uses. The method of the claimed invention enables a general approach toward the successful humanization of antibodies.

The prior art methods for producing humanized antibodies relied upon the presumed "self correcting" in assembling the CDRs on a new framework upon binding of the antigen; see, for example, Jones (**D1**), Verhoeyen (**D2**) and Riechmann (**D3**), all of which represent the work and strategy of the laboratory of Dr. Winter. As can be seen from those documents, the Winter laboratory preferred to use the framework from the variable region of the human NEWM antibody, the crystallographic structure of which was known,

see also Winter (**D15**) at page 17, 1st paragraph. It was their assumption that the framework of one and the same antibody can provide a passive scaffold onto which the CDRs from any other antibody may be grafted. Accordingly, when humanizing rodent monoclonal antibodies B1-8, D1.3 and YTH 34.5HL, respectively, Jones (**D1**), Verhoeyen (**D2**) and Riechmann (**D3**), all used the framework of the human NEWM antibody heavy chain as the acceptor, despite the fact that the donor antibodies had different antigen specificities.

The work of Riechmann (**D3**) did raise questions as to what extent the framework of a given antibody can provide a passive scaffold onto which the CDRs from another antibody may be grafted and retain their antigen binding affinity. However, in Riechmann (**D3**) antigen binding could be improved by particular considerations for the specific antibody investigated, so the general suitability of the acceptor heavy chain framework used, i.e., from the human NEWM antibody, was not questioned at all.

In contrast, the invention claimed in the contested Patent is based on the inventive concept that for producing humanized antibodies, the acceptor framework should be chosen to match the framework of the CDR donor antibody. Accordingly, when humanizing antibodies using CDR grafting, the claimed invention for the first time provided a criterion to select a framework which on its own is sufficient to retain antigen affinity, or for which at least the necessity of framework changes to retain antigen specificity is minimized. As shown in the post-published literature, it turned out that the chances of success with this method, i.e., that antigen specificity is retained with few or no framework substitutions, are considerably enhanced compared to the prior art approach. Hence, the method has been widely adopted.

Thus, the claimed invention contributes a method which on its own or optionally combined with further steps taught in the contested Patent leads toward the successful humanization of antibodies.

## 2. REQUESTS

### 2.1 General Requests

The Patentee requests that the oppositions be rejected and that the Patent be maintained on the basis of the new Main Request.

As an auxiliary measure, oral proceedings are requested in accordance with Art. 116(1) EPC. Furthermore, in order to expedite the proceedings, we request that an intermediate notice giving the preliminary view of the Opposition Division be issued in preparation for oral proceedings.

### 2.2 New Main Request

Claims 1 to 5 of the new Main Request correspond to claims 1 to 5 as granted.

Granted claim 6 has been deleted.

## 3. ALLEGED UNPATENTABLE SUBJECT-MATTER (ART. 100(A) EPC AND ART. 52 EPC)

Opponent II asserts that the claimed subject-matter comprises mental steps and therefore unpatentable subject-matter under Art. 52(2) EPC.

Opponent II's objection is unfounded. The claims relate to a method of producing a humanized immunoglobulin, i.e., to an industrial process, and therefore are of clear technical character. Opponent II seems to be of the opinion that steps 1 and 2 may be seen as mental steps which as such would not be patentable in view of Art. 52 EPC and that therefore the claims are unpatentable as well. However, there is no basis in the EPC for applying this so-called contribution approach for assessing patentability of a claimed subject-matter. The fact that one or more features of an otherwise claimed technical teaching relate to e.g. concepts, does not deprive the claim as such of technical character. In this context, we refer to recent decision T 931/95, "Controlling

pension benefits system/PBS PARTNERSHIP", dated September 8, 2000, not yet published in the OJ EPO, where the Board set out in catchword Nr. 4 that there is no basis in the EPC for distinguishing between "mental steps" of an invention and technical features when examining whether the invention concerned as a whole may be considered to be an invention within the meaning of Art. 52(1) EPC, thereby following the previous decisions T 1173/97, "Computer program product/IBM", OJ EPO 1999, 609.

In summary, there is no basis for the objection of Opponent II.

## 4. ALLEGED INADMISSIBLE BROADENING (ART. 100(C) EPC AND ART. 123(2) EPC, ART. 76(1) EPC)

### 4.1 Amended description

4.1.1 The term "CDR" in claim 1

Some of the Opponents allege addition of matter because of the paragraph [0012] of the printed specification of the contested Patent. They note that this passage was not in the patent application as filed and allege that it alters and adds to the meaning of claim 1.

The Patentee's position, as discussed in detail below, is that this passage was added only to provide the reader with additional scientific background on the structure of antibodies. It would have been clear to the skilled person that CDRs in claim 1 mean CDRs *as defined by Kabat*, a definition which is amply supported by the patent application. The passage does not put forward any definition of CDRs that combines the definitions of Kabat and Chothia; it merely notes that the Chothia definition is one way in which the term hypervariable regions or CDRs has been used.

That the cited passage does *not* in fact change the interpretation of CDRs in claim 1 from its intended meaning of CDRs according to the Kabat definition, may be seen from a large number of factors.

First, the added passage occurs only in the section of the Patent headed Background of the Invention, not in the Summary of the Invention nor the Detailed Description of the Invention nor the Experimental section. Importantly, nowhere does the contested Patent state that the Chothia definition is to be used in carrying out the invention, or in understanding the claims.

Secondly, the Opponents to the EP–B1 0 451 216 patent asserted at great length, and the Opposition Division agreed in its Reasons for Decision (**D50**), that Chothia (**D5**) did *not* provide an alternative definition of CDRs but rather gave a definition of hypervariable loops. After reviewing all the evidence, the Opposition Division concluded, "... the overwhelming majority of publications referring to CDRs correctly use this term as defined by *Kabat*," ((**D50**) page 22, last paragraph), and, "There is no convincing evidence for an alternative or refined definition of *Kabat et al.* CDRs by *Chothia et al.*...." ((**D50**) page 23, first paragraph under d5). It follows from this reasoning that the skilled person reading claim 1 would necessarily give the word "CDRs" in claim 1 its scientifically standard meaning of Kabat CDRs, there being nothing in the claim indicating that it should have the *non-standard* meaning of Chothia CDRs.

Thirdly, the skilled person would be reinforced in this understanding by the way in which claim 1 refers to "a humanized immunoglobulin (Ig) having complementarity determining regions (CDR's) from a donor Ig combined with a framework region from human Ig acceptor light and heavy chains" (emphasis added). Of course, the skilled person would already know what a humanized immunoglobulin was from the work of Dr. Winter and colleagues, e.g., Winter (**D15**) and Riechmann (**D3**), which are referred to in the Patent. But the humanized antibodies described by Dr. Winter always combined the CDR's *according to Kabat* with a human framework region. Hence, taking into account that the contested Patent certainly does not purport to give a new definition of humanized antibodies, the skilled person would expect the

meaning of CDRs in claim 1 to match that already used by Winter when describing humanized antibodies, namely the Kabat definition.

Fourthly, and especially importantly, the use of the word "framework" in claim 1 necessarily implies that CDRs mean *Kabat* CDRs. That is because the term "framework region" is given a clear and precise definition in the contested Patent:

> "As used herein, the term "framework region" refers to those portions of immunoglobulin light and heavy chain variable regions that are relatively conserved (i.e., other than the CDR's) among different immunoglobulins in a single species, as defined by Kabat et al., op.cit."; see Patent specification, page 6, lines 9 to 11 corresponding to page 12, lines 37 to page 13, line 3 of the divisional application as filed which is the identical paragraph of page 10, line 37 to page 11, line 3 of the application as originally filed.

Hence, the Patent unequivocably uses the *Kabat* definition for the framework region, i.e., the part of the variable region other than the Kabat CDRs. This same definition was given in the priority documents and the application as filed. But if the Kabat definition of framework is used, it only makes sense to also use the Kabat definition for the component with which the framework is to be combined, namely the CDRs. That alone would make it clear to the skilled person that CDRs in the claim must mean Kabat CDRs.

Finally, as extensively commented upon by the Opponents to the EP-B1 0 451 216 patent, other features of the specification make use of only the Kabat definition of CDRs. For example, in the construction of the exemplary humanized anti-Tac antibody, the donor CDRs that are transferred are defined according to Kabat (page 11, lines 28 to 29). Correspondingly, the CDRs underlined in the anti-Tac sequence are those of Kabat (page 4, lines 48 to 57, and Figs. 1 and 2 on page 16). Hence, the skilled person who turned to the experimental example in the contested Patent for guidance in carrying out the method of claim 1 would necessarily interpret CDRs according to the definition of Kabat.

In conclusion, for all these reasons, the term CDRs in claim 1 could only mean *Kabat* CDRs to the skilled person. Since the Kabat definition of CDRs was referenced in the patent application, there is no added matter in claim 1. Moreover, since the Kabat definition was also provided in the first and second priority documents, the contested Patent has priority to at least the second priority document, and in the view of the Patentee, to the first priority document as well.

4.1.2 The addition of references to prior art does not contravene Article 123(2) EPC

As explained in section 4.1.1, supra, the introduction of paragraph [0012] in the background section of the divisional application as filed does not provide a redefinition of "CDRs". It is a mere addition to the description of referenced prior art. This is already clear from the fact that the passage had been introduced into the background section of the specification. Furthermore, the paragraph in question at page 3, line 14 states that Chothia (**D5**) "have given an alternative definition of the hypervariable regions" based on the residues that constitute the loops in the three dimensional structures of antibodies. Indeed, the title of Chothia (**D5**) is "Canonical Structures for the Hypervariable Regions of Immunoglobulins". Thus, the discussion of Chothia (**D5**) in paragraph [0012] is an accurate representation of the teaching of Chothia (**D5**), although, like a few scientific publications, it also refers to the Chothia hypervariable regions as Chothia CDRs. The paragraph merely reflects that besides the original definition of the hypervariable regions that determine complementarity by amino acid sequence variability, an alternate definition of the hypervariable regions had been given based on structural considerations; see also the introduction of Chothia (**D5**).

From the case law of the Boards of Appeal, it is clear that such addition of discussion of background art to the description can not be interpreted as the addition of subject matter; see Headnote V of the leading decision

T11/82,"Control circuit/LANSING BAGNALL", OJ EPO 1983, 479. This principle was recently confirmed by decision T450/97, "Shampoo composition/PROCTER & GAMBLE", OJ EPO 1999, 67, where the Board explicitly stated in the Headnote that "the mere addition of a referenced prior art does not contravene Art. 123(2) EPC".

Thus, there is no basis for the objections of the Opponents.

**4.2 Design versus production**

Opponent II alleges that the parent application as originally filed relates to the "design" of humanized antibodies rather than to the production of such antibodies.

The Opponent's objection is unfounded. Already at the outset of the application as filed, it is stated that the invention relates generally to the production of a non-immunogenic antibody, see the application as originally filed at page 1, lines 4 to 8. Likewise, the application describes in great detail on page 16, line 12 to page 20, line 30 how recombinant DNA methods are used to produce the antibodies. The fact that the term "design" had been used in the original claims cannot of course change the fact that the originally disclosed methods of the invention comprise true process steps. Hence there can be no doubt that the application as filed relates to the production of humanized antibodies, which indeed is what the invention as described and claimed in the original application is all about.

For the above reasons, the objection of Opponent II is off the mark.

## 5. ENABLING DISCLOSURE (ART. 100(B) EPC AND ART. 83 EPC)

### 5.1 The claimed subject matter is sufficiently disclosed

5.1.1 The Patent provides sufficient guidance for obtaining humanized antibodies with high binding affinity

The Opponents have pointed out that the method of claim 1, comprising the selection of human acceptor frameworks that have at least 65% homology to the donor frameworks, is not generally *itself* sufficient to ensure high binding affinity of the humanized antibody. They have pointed to the Chung Declaration (**D11**), which was filed by the Patentee during opposition proceedings to EP-B1 0 451 216. This declaration reported that a version of the humanized anti-Tac antibody which had no donor substitutions in the framework did not have detectable binding affinity. In this regard, the Patentee agrees with the factual assertions of the Opponents, but not with their conclusions.

Claim 1 covers a *method* "comprising" certain steps, which implies that additional steps may also be used to yield an optimal product. The claim makes no assertion that the claimed steps alone are sufficient to produce a humanized antibody that has any particular affinity for antigen. The proper question in judging enablement is whether the method of claim 1 can in fact be carried out over the full scope of donor antibodies. Although there may be some minor quibbles on this point relating to the nature of the collection of human Ig chains and the comparison method used, which will be dealt with below, the Opponents have not seriously disputed this.

Claim 1 solves the technical problem over its full scope. That is, for *any* donor antibody, the claim provides a method of selecting the human acceptor light and heavy chain frameworks to be combined with the donor CDRs, so that after optional donor substitutions are made in the framework, the humanized antibody possesses therapeutically useful binding affinity while exhibiting acceptable immunogenicity in human patients. The

specification of the patent provides ample information, namely Criteria II – IV on page 7, by which those optional donor substitutions may be determined. In neither the opposition to the parent patent nor to the current patent, have the Opponents been able to provide *any specific example* of an antibody which could not be successfully humanized according to the teachings of the patent.

5.1.2 The claimed method is an advancement of CDR grafting

The principle of producing humanized antibodies by CDR grafting was known for example from Winter (**D15**) and its corresponding scientific publications Jones (**D1**) and Verhoeyen (**D2**), as well as Riechmann (**D3**). In this context, we would like to point out that the general CDR-only grafting method of Winter (**D15**) matured into a patent with substantially broad claims. Thus, the EPO was apparently of the opinion that Winter (**D15**) generally enabled the production of humanized antibodies by CDR grafting. Furthermore, although the Winter patent had been opposed, enabling disclosure was not a ground of the opposition. Thus, even the Opponent (Celltech, which is also Opponent V in the current proceedings) acknowledged enabling disclosure of the Winter patent (**D15**).

Moreover, the Jones (**D1**), Verhoeyen (**D2**) and Riechmann (**D3**) references are cited by the Opponents as closest prior art for the assessment of inventive step. In order to qualify as relevant prior art, a given document must of course provide an enabling disclosure. Documents (**D15**) and (**D1**), (**D2**) and (**D3**) according to the Opponents provide an enabling disclosure for the production of humanized antibodies at least to some extent. However, they have in common that they lack steps (1) and (2) of claim 1 of the contested Patent. These additional steps provide an improvement of the prior art methods for producing humanized antibodies, since as we will discuss below, the additional process steps considerably enhance the chances to obtain humanized antibodies with a useful binding affinity. In any case, it is untenable to argue that a method which comprises more process features than corresponding methods in the prior art is not enabled while the

prior art methods are. And as will be discussed in section 9, infra, the scientific community acknowledged the contribution of the method of the invention as providing a key step towards successful humanization of antibodies.

Hence, the Opponents' general objections to the claimed method for alleged lack of enabling disclosure cannot stand a closer scrutiny. The only issue that may be discussed in cases where an invention provides a further development of a method is whether the new process feature is enabled. Indeed, some of the Opponents made such objections to steps (1) and (2) of claim 1. However, as we will show below these objections are unfounded as well.

## 5.2 Alleged missing essential features

### 5.2.1 Alleged insufficiency with respect to homology

Opponent V (page 6) alleges that the skilled person could not perform the method of claim 1 because the patent provides no definition of homology.

In addition, several Opponents have alleged that the word "homology" in claim 1 is unclear. They assert that when the percent homology of two sequences is calculated, pairs of amino acids that have similar characteristics (i.e., are "homologous") are counted as matches and thus contribute to the percentage of homology. Since the contested Patent does not specify which pairs of amino acids are considered to be "homologous", they conclude that the term percent homology lacks clarity. Lack of clarity is not a ground of opposition, but this issue may be relevant to novelty, inventive step and sufficiency of disclosure.

It is the Patentee's position, which will be supported by multiple citations below, that when referring to sequences, "percent homology" normally *means* "percent identity," and the term is so used and understood by the vast majority of skilled persons. Hence, the question of which amino acids

should be counted as matches in claim 1 never arises; only *identical* pairs count toward the percent homology. Indeed, as also discussed below, in the context of the contested Patent, this would have been the only sensible interpretation of percent homology. The Opponents have noted that claim 1 and granted claim 6 of the Patent respectively refer to 65% homology and 65% identity, and they infer that the Patentee must have intended percent homology and percent identity to mean something different. *This inference is completely unwarranted.* Rather, the Patentee felt free to use percent homology in one place and percent identity in another place because he (and, as shown below, other skilled persons) consider them to be *synonymous*.

The Patentee's position is supported, in the first place, by the dictionary definition of homology as given for example in the standard reference work, Dictionary of Biochemistry and Molecular Biology (**D51**):

> "**sequence homology** The identity in sequence of either the amino acids in segments of two or more proteins, or the nucleotides in segments of two or more nucleic acids"; see (**D51**), at page 437, first column.

Hence, homology between protein sequences is to be calculated by determining the identity of amino acids; nothing in this standard definition permits the inclusion of amino acids that are only similar.

This dictionary definition is in fact used by most scientists. As a first example, we cite Gorman (**D52**). As discussed in section 9, infra, this scientific publication is significant because it showed that the homology-based method of claim 1 was successful in humanizing a particular antibody, whereas the earlier method of Dr. Winter and colleagues was not. Gorman (**D52**) states:

> "The $V_H$ region of KOL was chosen because of all known human heavy chain V regions its overall amino acid sequence is very homologous to the Campath-9 $V_H$ region (Fig. 1A) containing 72% identical residues ... By

> contrast, the NEW $V_H$ region sequence has only 47% identical residues. We reasoned ... we could maximize the chances of retaining correct CDR structure (and hence antigen affinity) by deriving framework sequences from a human $V_H$ region that is most homologous to that of the rodent"; see (**D52**), page 4182, last paragraph, to page 4183, first paragraph (emphasis added).

This passage is not only an excellent restatement of the approach of the contested Patent, but clearly shows that Gorman (**D52**) uses percent identity to measure the extent of homology. Even more explicitly, Gorman (**D52**) later states:

> "The KOL $V_H$ region has a 72% homology to Campath-9 $V_H$ region, whereas the NEW $V_H$ framework has only 47% homology"; see (**D52**) at page 4184, first paragraph (emphasis added).

Hence, Gorman (**D52**) refers to the exact same sequences as having "72% identity" in one paragraph of their paper and having "72% homology" in another paragraph (and similarly for "47% identity" and "47% homology"). Beyond doubt then, the skilled authors of Gorman (**D52**) consider percent homology to be *synonymous* with percent identity, and feel free to use the terms interchangeably, in conformance with the Patentee's position.

As a second example, we refer to Chothia (**D9**), which was published in 1986 and has the same two authors as the Chothia (**D5**) paper where the Chothia definition of hypervariable regions was presented. In connection with the latter article, it has been observed that Dr. Chothia is an eminent scientist who is very careful about the meaning of the words he uses. So the following two passages respectively from the Results section and Conclusions section of Chothia (**D9**) are especially significant:

> "Pairs whose sequence identity is > 50% have 90% or more of the residues of the individual structures within the common cores. Pairs whose residue identity drops to about 20% have common cores that contain between 42% and 98% of the residues of individual structures

(Table II, Figure 1)"; see (**D9**) at page 824, second paragraph (emphasis added).

"A protein structure will provide a close general model for other proteins with which its sequence homology is > 50%. If the homology drops to 20% there will be large structural differences that are at present impossible to predict"; see (**D9**) at page 826, first paragraph (emphasis added).

The text of Chothia (**D9**) (see, e.g. Table II) and the commonality of the key numbers 50% and 20% between these two passages makes it clear that Dr. Chothia uses "sequence identity" and "sequence homology" to mean *exactly the same thing*, that is, he calculates the percent homology by determining the percent of residues that are identical between two sequences, in accordance with the view of the Patentee.

To prove that the approach of Gorman (**D52**), Chothia (**D9**) and the Patentee was and still is the overwhelmingly preferred approach of those skilled in the art, we submit the Declaration of Mr. Wiesner, a specialist in bioinformatics (**D61**). Mr. Wiesner used a search of the National Library of Medicine Medline data base of biomedical journals to find scientific papers which use the term "percent homology" or related terms in their abstract. He then obtained these articles, which had publication dates from before the filing date of the contested Patent up to the current time, and studied them to determine what the authors meant by "percent homology".

As described in detail in his Declaration (**D61**), Mr. Wiesner analyzed 28 articles. In the vast majority of them – 25 – he found that the authors used percent homology to mean percent identity. In a few of these publications, the authors themselves explicitly or implicitly stated this. For the remaining papers, it was possible to prove that the authors used percent homology to mean percent identify by actually determining the percent identity between the relevant sequences, and showing it was equal to what the authors called percent homology. The fact that so many authors used the term percent homology to mean percent identity without even stating this in their papers

*clearly demonstrates that they expected their readers to know that percent homology means percent identity.*

Mr. Wiesner did find 3 articles where the authors defined percent homology to include pairs of amino acids that were similar but not identical. However, in each case, the authors specifically *stated* that they were using the term percent homology in this manner. This contrasts with the situation described above when percent homology means percent identity, which authors usually leave unstated. It is thus clear, not only that percent identity is the overwhelmingly preferred definition of percent homology, but it is the *default* definition. That is, percent homology means percent identity unless the author specifically provides a different definition. Notably, no such alternate definition of percent homology was given in the contested Patent. Hence, the skilled person would certainly have understood percent homology in claim 1 to mean percent identity.

To support a contrary position on the meaning of percent homology, Opponent I presents (page 12) the output of a sequence comparison made with the widely used BLAST 2 algorithm (**D7**). Opponent I refers to this as a "sequence homology plot" (page 12, paragraph 4.9.4) and notes that it includes matches of similar amino acids. However, what Opponent I fails to point out, but which is obvious from an inspection of (**D7**), is that nowhere does the BLAST 2 program present its output as "percent homology". The term "sequence homology plot" in reference to the BLAST 2 output is thus a creation of Opponent I – in fact, *the word homology does not even appear in (**D7**)*. Rather, BLAST 2 merely refers to the number of similar pairs of amino acids as "positives". Hence, all that Opponent I has really shown is that some scientists find this number to be of interest, and therefore a computer program has been written to determine it – which is in no way denied by the Patentee. What *is* vigorously denied by the Patentee is that skilled persons normally refer to the percent of similar amino acid pairs as percent homology. The Patentee's position on this is in fact *supported* by the absence of the word "homology" from the BLAST 2 output.

The same situation holds true with other widely used computer programs for comparing sequences. For example, the Wiesner Declaration (**D61**) includes output from the Wisconsin Package for sequence analysis (see (**D61**), Exhibit 3). As may be seen there, the percent of similar amino acids is (logically) called "Percent Similarity" – it is *not* called percent homology. It is also worth noting that when the percent of similar amino acids is of interest, the computer program generally inserts in the sequence alignment a special symbol between pairs of amino acids that are similar. For example, BLAST 2 inserts plus signs (see (**D7**)), whereas the Wisconsin Package inserts colons (see (**D61**), Exhibit 3). In striking contrast, the sequence alignments in the contested patent (page 16, Figs 1 and 2) have a symbol (a vertical line) *only between identical amino acids* (see the figure legends on page 4, lines 48 to 57). Indeed, the percent homology between the frameworks of the donor and acceptor sequences for humanized anti-Tac can be determined merely by counting the number of vertical lines outside the CDRs, and dividing by the total number of framework amino acids (giving the result 58/87 = 67% for the heavy chain and 52/80 = 65% for the light chain). Hence, if the skilled person had any remaining doubt about the meaning of percent homology in the contested Patent, the key Figure 1 would have made clear that it must mean percent identity.

For the above reasons, it is submitted that the meaning of "percent homology" in claim 1 is clear to the person skilled in the art.

5.2.2 Alleged insufficiency with respect to "collection"

Opponent VI (page 10) alleges that claim 1 is insufficient because it does not specify the collection of sequences from which the comparison is to be made. However, the person of skill in the art would certainly have been aware of such collections, for example, the comprehensive collection of Kabat (**D4**), a reference which is cited in the contested Patent. The Patent also specifically cites another collection that could be used, the National Biomedical Research Foundation Protein Identification Resource (page 6, lines 42 to 44), and provides yet further guidance by stating that typically the

collection will be "representative" and contain at least "10 to 20" distinct human heavy chains and similarly for light chains (page 6, lines 53 to 55). In fact, claim 1 could be carried out with any of these collections, and the skilled person would have no difficulty selecting one based on availability, convenience. etc. No more than that is required.

Opponent V (page 8) notes that different human antibody sequences might be chosen as acceptor depending on which collection was used for comparison. But so what? Any of the sequences selected according to the method of claim 1 would be satisfactory. Surely nothing requires that the method provide only a single solution to the problem of humanizing a particular donor antibody.

The decisive fact is that the contested Patent teaches which framework region to select as the homologous acceptor framework, and that such framework regions were available at the priority date of the contested Patent. The Opponents have not disputed this. If later a more homologous framework became available, then the person skilled in the art might prefer to select it, or to search other available data bases for comparable frameworks. In this context, we refer to the Decision in the opposition proceedings concerning European Patent EP-B1 0 549 581, where the Opposition Division had no doubt that the person skilled in the art had no problems with selecting homologous frameworks from any data base despite the fact that the number and content of such data bases change all the time; see section 7, last full paragraph on page 7 of the written decision concerning EP-B1 0 549 581 dated February 11, 2000.

5.2.3 Alleged insufficiency with respect to form of comparison

Opponent V (page 5 to 6) alleges that claim 1 is insufficient because it allows a choice of comparing frameworks or variable regions, and the skilled person would not have known which to choose. However, the mere fact that a claim envisages two alternative ways of performing a function certainly does not make it insufficient. In fact, either type of comparison would be

satisfactory, since comparing variable regions necessarily encompasses comparing the framework regions that are contained within them. And despite the Opponent's allegations, there is no ambiguity at all regarding what region must have at least 65% homology, since claim 1, step 2 specifies that the 65% homology be with "the respective donor framework sequences". The reason that the claim provides the option of comparing the entire variable regions is that many sequence data bases contain listings of variable regions rather than just their framework portions.

## 6. ENTITLEMENT TO DIVISIONAL STATUS (ART.76(1) EPC)

In section 4.8 of its opposition brief, Opponent I questions the divisional status of the contested patent because the paragraph [0012] was also present in the divisional application as published. In view of its submission under Art. 123(2) EPC, the Opponent concludes that the divisional application cannot be deemed to have been filed on the date of the parent application and that it is not entitled to any right of priority.

However, as discussed in detail in section 4.1.2, supra, the introduction of the paragraph in question does not amount to an inadmissible broadening but merely was an addition of reference to prior art in accordance with Rule 27(1) (b) EPC. As has been confirmed by the Technical Boards of Appeal, such addition of reference to prior art can be made at any time and even in a granted patent at the opposition stage without extending the disclosure beyond the content of the application as originally filed. Thus, Opponent I's submissions concerning entitlement to the divisional status are unsubstantiated for the same reasons as discussed in section 4.1.2, supra.

Accordingly, the divisional application and the granted patent are entitled to the filing date of the application as originally filed and enjoy the right of priority to the US applications filed on December 28, 1988 and February 13, 1989.

## 7. PRIORITY (ART. 87 AND 88 EPC)

As discussed in section 6, supra, the contested patent is entitled to divisional status and therefore is also entitled to claim priority of US applications US 290975 and US 310252 filed on December 28, 1988 and February 13, 1989, respectively.

Some of the Opponents object that the patent is not entitled to the first priority. Without conceding that this is correct, Patentee leaves this issue aside for the moment, since at present it is not relevant for the purpose of novelty and inventive step of the claimed invention.

On the other hand, it appears as if there is general agreement that the contested Patent enjoys the second priority date of February 13, 1989. For the sake of completeness, we refer to corresponding support for claim 1 in the second priority document; see, e.g., on page 3 the paragraph following the title "Summary of the Invention", and the discussion of criterion I starting at page 10 and continuing on page 11, the first full paragraph of which again explicitly recites the 65% homology criterion.

## 8. NOVELTY (ART. 100(A) EPC AND ART. 54 EPC)

As discussed in section 7, supra, the contested Patent and the claims are entitled to at least the second priority date, February 13, 1989. Consequently, the Patentee's parent patent application EP-A 0 451 216 and Queen (**D6**) do not belong to the prior art under Art. 54(1)(2) EPC. No further discussion of those documents is needed.

### 8.1 Novelty over Winter (D15) and Verhoeyen (D2)

Example 2 of Winter (**D15**) describes the humanization of the heavy chain of the D1.3 anti-lysozyme antibody; Verhoeyen (**D2**) is the scientific publication corresponding to this patent application and describes the same humanized heavy chain. Several Opponents have cited these references with regard to

novelty, asserting that the heavy chain frameworks of the mouse donor D1.3 and human acceptor NEWM antibodies are 65.5% or 66% identical, which is greater than the 65% criterion in claim 1.

First, even if this were true, these documents would not destroy the novelty of claim 1, which contains other essential features not found in Winter (**D15**) or Verhoeyen (**D2**). Specifically, claim 1 describes a method of producing a humanized immunoglobulin (Ig) in which the *light* chain as well as the heavy chain has a human framework, i.e., is humanized. However, neither Winter (**D15**) nor Verhoeyen (**D2**) discloses a humanized D1.3 light chain. Moreover, claim 1 specifies that the donor light and heavy chain sequences be compared with sequences in a collection of human Ig chains, but no such comparison is performed or implied in the cited documents, even for the heavy chain.

Furthermore, the assertion that the donor D1.3 and acceptor NEWM heavy chain frameworks are more than 65% identical is not correct. To make this clear, we have generated Exhibit 1 (**D53**) to these Observations, which compares the relevant sequences taken directly from Winter (**D15**). As can be seen from (**D53**) and its legend, the sequences are 64.4% identical, so do not have "at least 65% homology" as required by claim 1. The Opponents apparently derive a higher figure by considering the Q and X at the first positions of the respective sequences to be identical. However, this is absurd on its face: the symbols Q and X are not identical, and X is not a "wildcard" that can be matched to any other amino acid that the Opponents choose. (Rather, X means that the actual amino acid is unknown). Finally, putting the matter beyond doubt, the authors of Winter (**D15**) and Verhoeyen (**D2**) have *themselves* determined and published the number of matches between the D1.3 and NEWM frameworks, stating:

> "Nevertheless, the grafting of hypervariable regions from mouse to human framework regions is sufficient to transfer the lysozyme-binding site, an extensive surface of interaction, despite the 31 of 87 residues that differ

between the heavy-chain framework regions"; see (**D2**) at page 1535, first paragraph (emphasis added).

Clearly, if 31 of 87 amino acids differ, then 87 minus 31, or 56, are the same, so the percent identity is 56/87 = 64.4%, which is completely consistent with the calculations of the Patentee.

## 8.2 Novelty over Riechmann (D3) and Clark (D14)

Riechmann (**D3**) describes the humanization of both the heavy and light chains of a rat antibody against the CAMPATH-1 antigen. Although the initial humanized antibody made in this way lost much of its binding affinity, this was largely restored by making substitutions in Chothia hypervariable loop H1. Clark (**D14**) is a patent application based on the same work.

These documents do not disclose the method of claim 1. Specifically, that method comprises in step 1 "comparing the framework or variable region amino acid sequences of the donor Ig light and heavy chains with corresponding sequences in a collection of human Ig chains." No such comparison is made in Riechmann (**D3**) or Clark (**D14**) for *either* the light or heavy chain. In fact, these documents only mention a *single* human heavy chain, that of the NEW antibody, not a collection of such chains. Moreover, the only heavy chain comparison made is between the donor and *reshaped* (humanized) chains, not the donor and *acceptor* chains (see legend to Fig. 1a on page 324 of Riechmann (**D3**), and the corresponding Fig. 2a of Clark (**D14**)). And while these documents mention two human light chains, NEW and REI, the NEW light chain was immediately dismissed "because there is a deletion at the beginning of the third framework region in NEW" (first paragraph of second column on page 325 of Riechmann (**D3**)). Hence, there is not even a hint that comparisons were made with the donor sequence before selecting the REI chain.

Finally, for completeness, we have ourselves compared in Exhibit 2 (**D54**) the heavy chain sequences of the rat donor antibody and human acceptor

antibody used by Riechmann (**D3**). As can be seen from (**D54**) and its legend, the framework sequences are only 53% homologous.

### 8.3 Novelty over Huston (D19)

Opponent V cites Huston (**D19**) against the novelty of claim 1. However, this citation is subject to the same objections as made above against Verhoeyen (**D2**) and Riechmann (**D3**). Huston (**D19**) does not describe any collection of human Ig chains but only presents again the human NEWM antibody. Still less does Huston (**D19**) disclose or even suggest that the donor mouse glp-4 sequences (page 40, third paragraph to page 41, second paragraph) be compared against the sequences in any such collection, as required by claim 1. Yet other arguments can be made against the relevance of Huston (**D19**) to novelty, for example, that Huston (**D19**) does not even disclose a humanized immunoglobulin, but only what he calls a biosynthetic antibody binding site (BABS), but these arguments are superfluous in light of the above.

## 9. INVENTIVE STEP (ART. 100(A) EPC AND ART. 56 EPC)

Any one of documents Jones (**D1**), Verhoeyen (**D2**), Riechmann (**D3**) and Winter (**D15**) may be seen as a candidate for the closest prior art. All these documents have in common that they teach to use the human NEWM antibody as source for the acceptor framework, at least for the heavy chain of their humanized antibody. However, no criteria have been taught how to select human acceptor frameworks other than those of the NEWM antibody or the one example with the REI antibody for the light chain in (**D3**). Furthermore, as is shown for example in Gorman (**D52**), the use of the NEWM based framework may result in very poor antigen binding.

The objective problem to be solved, in light of the methods disclosed in the prior art, can thus be considered to be the provision of further guidance in the process of humanizing antibodies, preferably improving the effectiveness of retaining antibody affinity.

A solution to this problem is provided by the method of claim 1, i.e., the use of a human acceptor framework the amino acid sequence of which has at least 65% homology with the framework sequences of the respective donor antibody. As already discussed in section 5, supra, the solution provided by the method of claim 1 has been generally acknowledged as means towards the successful humanization of antibodies. Furthermore, post-published documents such as Gorman (**D52**) demonstrate and confirm that the use of homologous human acceptor framework sequences maximizes the chances of retaining antigen affinity; see also section 9.6, infra. Accordingly, the problem has been solved by the invention claimed in the contested patent.

In the following we will show that none of the cited documents teaches or suggests to the person skilled in the art to perform steps (1) and (2) of claim 1 in order to solve the problem posed.

### 9.1 Inventive step over Jones(D1), Verhoeyen (D2) and Riechmann (D3)

Jones (**D1**), Verhoeyen (**D2**) and Riechmann (**D3**), which have been cited by the Opponents, were the three scientific papers presenting humanized antibody chains that were published before the priority date of the contested Patent. All three articles emanated from the laboratory of Dr. Winter. The Patentee submits that these papers practiced humanization in a consistent way that was quite different from the homology-based method claimed in the Patent, and which indeed taught directly away from any such method.

#### 9.1.1 Jones (D1)

The first paper in this series was Jones (**D1**), in which the authors explained their choice of the human NEWM antibody heavy chain as acceptor this way:

> "We grafted the CDRs from the $V_H$ domain of the mouse monoclonal antibody B1-8 (ref. 7) into the $V_H$ domain of

> the human myeloma protein NEWM, whose crystallographic structure is known"; see (**D1**) at page 523, first full paragraph.

Hence, Jones (**D1**) apparently chose NEWM as acceptor because its 3-dimensional structure was known, and indeed that structure was extensively used in their paper (see, e.g., Fig. 1, which presents several stereo views of the structure). There is not the slightest mention that any other human antibody heavy chain was considered as acceptor, or that high homology was a factor in the choice of NEWM, or even of what the extent of homology between donor and acceptor frameworks actually was (it may readily be calculated to be 56%, well below the 65% criterion of claim 1).

9.1.2 Verhoeyen (**D2**)

Verhoeyen (**D2**) also utilizes the human NEW antibody for the acceptor and notes "the crystallographic structures of both parent antibodies are known ...," where the "parent" antibodies refer to the donor D1.3 and acceptor NEW antibodies ((**D2**), page 1535, second column). Again, there is not the slightest suggestion that the NEW heavy chain was selected from a larger collection based on its homology to the donor, or that the percent homology should be calculated or was in any way relevant. (Although Jones (**D1**) and Verhoeyen (**D2**) use the same human antibody as acceptor, unfortunately Jones (**D1**) refers to it as NEWM and Verhoyen (**D2**) as NEW. That these are in fact the same antibody is known because (i) the frameworks of the humanized chains in Fig. 2b of Jones (**D1**) and Fig. 2 of Verhoyen (**D2**) are identical, and (ii) Verhoeyen (**D2**) even references Jones (**D1**) as the source of the NEW heavy chain ((**D2**), page 239, last complete sentence of the second column)).

9.1.3 Riechmann (**D3**)

Finally, Riechmann again utilizes the "crystallographically solved" ((**D3**), page 325, second column) NEW antibody to provide the acceptor heavy chain, once again without consideration of any other human antibodies or of

homology. The authors' choice of antibody to provide the acceptor *light chain* is even more informative, since they state:

> "The REI light chain was used <u>because</u> there is a deletion at the beginning of the third framework region in NEW"; see (**D3**) at page 325, second column (emphasis added).

The clear implication of this statement is that the authors would have *preferred* to use the NEW light chain, and did not do so only because of the deletion. However, the light chain frameworks of the donor antibody and the NEW antibody have a low homology of only 52%, whereas the light chain frameworks of the donor antibody and the REI-based antibody actually used as acceptor have much higher homology (as may readily be calculated after aligning the published sequences). Hence, Riechmann (**D3**) would actually have preferred to use the light chain with *lower* homology (below 65%), and was only prevented from doing so by the deletion. This shows beyond any doubt that Winter and his colleagues gave no consideration to the extent of homology, and that homology played no role in their method of humanization.

Where would this leave the skilled person attempting to humanize an antibody after the publication of the three prior art papers from Dr. Winter's laboratory, but before the teachings provided by the contested Patent? Such a person would necessarily turn to Dr. Winter's papers to learn to humanize an antibody – where else should he or she turn, no other antibodies having been at that time humanized? The skilled person would then learn that Dr. Winter's group had always used the *same* antibody to provide the human acceptor heavy chain – the NEW antibody. Moreover, each time, Dr. Winter and colleagues had been notably successful, albeit in Riechmann (**D3**) they needed to make a substitution in the Chothia hypervariable H1 loop to regain affinity. Surely, the person skilled in biotechnology, who is by definition <u>conservative</u> and <u>cautious</u> (<u>T455/91</u> at section 5.1.3.3), would have followed the leaders in the field and used the same NEW antibody heavy chain rather than setting out to do something different. And even,

*arguendo*, had the skilled person wanted to use an acceptor antibody other than NEW, what he or she would have learned from the relevant prior art was that it is important to use an acceptor antibody whose crystallographic structure is known, *not* that the extent of homology has anything to do with the matter.

## 9.2 Inventive step over Winter (D15)

Winter (**D15**) is the patent application corresponding to Jones (**D1**) and Verhoeyen (**D2**); it presents no other examples of humanization. However, the Opponents have cited the following quotation from Winter (**D15**):

> "It may be necessary only to transfer those residues which are accessible from the antigen binding site, and this may involve transferring framework region residues as well as CDR residues"; see (**D15**) at page 7, fourth paragraph.

To the extent that the skilled person might have learned anything from this rather brief and ambiguous remark, it would have been that it might be necessary to use *donor* amino acids in addition to the Kabat CDRs when humanizing an antibody. There is nothing whatever here that is relevant to how the *acceptor* antibody is chosen; in fact the entire text of Winter (**D15**) never suggests the necessity or even the desirability of considering acceptor antibodies other than NEW. The Opponents claim that Winter (**D15**) would have made it obvious to select, from available human antibodies, an acceptor with high homology to the donor. *But if it was obvious, why wasn't it obvious to Dr. Winter, who did no such thing*? It is absurd to suppose that it would have been obvious to one of ordinary skill in the art, when it wasn't obvious to the acknowledged leader in the field.

Indeed, after filing Winter (**D15**), when Dr. Winter and colleagues humanized another antibody in Riechmann (**D3**), they once again used the NEW antibody heavy chain as acceptor, although it only had 53% homology to the donor. Clearly, Dr. Winter himself had found no instruction in his own

patent application to select an acceptor framework with high homology to the donor. Even more conclusive is what the authors of Riechmann (**D3**) did when their initial attempt at humanizing the anti-CAMPATH-1 antibody lost most of its binding affinity. They did *not* even try making another humanized antibody using a more homologous framework. Rather, they made substitutions in Chothia hypervariable loop H1 that restored affinity. This procedure, rather than anything to do with homology, is all that the skilled person could have learned from the combination of Winter (**D15**) and Riechmann (**D3**).

### 9.3 Inventive step over Chothia (D5)

Chothia (**D5**) analyzed the structure of a number of antibodies, provided a new definition of hypervariable regions or loops, and proposed that these hypervariable regions could adopt only a limited number of canonical conformations. Certain Opponents infer that since these canonical conformations depend on particular amino acids in the antibody, it would have been obvious to the skilled person that these amino acids should be the same in the donor and acceptor antibodies, which could be achieved by choosing an acceptor with high homology to the donor.

However, what Chothia (**D5**) actually says is:

> "The descriptions of the hypervariable regions given above suggest that their main-chain conformations are determined solely by particular residues within each region"; see (**D5**) at page 913, first paragraph of section 10.

Contrary to the assertions of the Opponents, this statement would clearly have told the skilled person not to worry about amino acids outside the hypervariable regions (i.e., in the framework), because the hypervariable regions already contain the information that determines their conformation. Moreover, to the extent that any amino acids in the framework do impact on the conformation of the hypervariable regions, these residues are highly

conserved between different antibodies, as pointed out in the Levitt Declaration ((**D55**), Section 15). For example, see the statements regarding conservation of residues in Chothia ((**D5**), page 907, first and second paragraphs). Hence, these amino acids would generally not be changed when humanizing an antibody, and would not be of concern to the humanizer.

These arguments are supported by the known relationships between the Winter and Chothia laboratories. Verhoeyen (**D2**) thanks Chothia and his co-author Lesk for discussions and comments (see (**D2**), page 239, footnote 23), and both Verhoeyen (**D2**) and Riechmann (**D3**) reference Chothia (**D5**). But as discussed above, neither Verhoeyen nor Riechmann suggest that it is preferable to use a more homologous acceptor. If Dr. Winter and his colleagues did not deduce this from Chothia (**D5**), is it believable that the person of *ordinary* skill would have done so? Similarly, but in the other direction, there is no statement in Chothia (**D5**) referring to humanization. And even the later paper Chothia (**D10**), published *after* Verhoeyen (**D2**) and Riechmann (**D3**), while providing further support for the original observations of Chothia (**D5**), again said nothing about humanization. If Dr. Chothia did not write that his work was relevant to humanization, *at the time*, why should the person of ordinary skill have deduced this?

## 9.4 Inventive step over Cheetham (D16)

Opponent V asserts (page 20-21) that the contested Patent lacks inventive step over Cheetham (**D16**) in view of Riechmann (**D3**) and Verhoeyen (**D2**). In response, it is to be noted first that Cheetham (**D16**) is a review article describing the earlier work of Jones (**D1**), Verhoeyen (**D2**) and Riechmann (**D3**); no new humanized antibodies or methods of humanization are presented by Cheetham (**D16**). While Cheetham (**D16**) comments that the work of Riechmann (D3) is in the realm of "tinkering" rather than "tailoring" ((**D16**), page 172, first line of second column), this remark does not go beyond what is already in Riechmann (**D3**), and certainly adds nothing to the skilled person's knowledge of how to humanize antibodies. At most

Cheetham (**D16**) alerted the skilled person that there may be difficulties in humanization, without making any contribution to solving them.

In fact, Dr. Cheetham wrote a 2500-word article reviewing all the then-published papers on humanization yet never suggested anything remotely related to the homology-based method of the contested Patent; the words "homology" or "identity" are not even used in Cheetham (**D16**). But Dr. Cheetham, who reviewed the field for a major journal, was certainly of at least ordinary skill in the art. Hence, the omission of any suggestion of the claimed method in Cheetham's important review article is powerful contemporaneous evidence that the method was *not* obvious to one of ordinary skill. This evidence is even further supported by another 1988 article, Verhoeyen (**D56**). That article, which was authored by two early workers in humanization, Verhoeyen and Riechmann, also reviewed humanization technique (page 76, third column) but again made no mention of homology. The only reasonable conclusion is that *Cheetham, Verhoeyen and Riechmann did not mention the relevance of homology in any of their papers because they did not think of it before the contested Patent, and neither would the ordinary skilled person have done so.*

## 9.5 Inventive step over Amit (D20), Sheriff (D21), Davies (D22) and Panka (D23)

Opponent V asserts that the contested Patent lacks inventive step over Amit (**D20**), Sheriff (**D21**), Davies (**D22**) and Panka (**D23**) in view of Riechmann (**D3**) because these papers suggest the importance of framework residues to antigen binding. However, in the opposition to the patent EP-B1 0 451 216, the Patentee submitted declarations from Dr. Panka, the first author of Panka (**D23**), and from Dr. Poljak, the senior author of Amit (**D20**), which are resubmitted here as Panka Declaration (**D57**) and Poljak Declaration (**D58**). These Declarants showed that their own papers were not relevant to humanization and were certainly insufficient to teach how to humanize antibodies, and Dr. Poljak made similar comments about Sheriff (**D21**).

Davies (**D22**) is a review article largely based on the work of Amit (**D20**) and Sheriff (**D21**) and goes no further.

Furthermore, even if these papers had suggested to the skilled person that some amino acid in the framework was important to humanization (which is denied), there is still a huge gap between any such notion and the homology-based method of the contested Patent. Indeed, choosing a more homologous acceptor antibody cannot even ensure that a desired amino acid will be found at any particular position in the framework sequence.

## 9.6 How those of skill in the art viewed the Invention

Those skilled in the art clearly considered the method of the contested Patent to be new and important. For example, Dr. Adair, who at the time was employed by Celltech (a competitor of the Patentee and now one of the Opponents to the contested Patent) wrote the following in 1992:

> "An alternative procedure for the identification of these important non-CDR residues has been described (Queen and Selick 1990). In this procedure, the murine variable region sequences are compared to available human sequences and the human sequence with the highest homology is taken as the acceptor framework....
>
> This approach of using highly homologous human antibody sequences as the starting acceptor framework, and then also including, as necessary, other residues from outside of the CDR regions has been used successfully to humanize the anti-human CD3 antibodies YTH12.5 (Routledge et al. 1991) and UCHT1 (Shalaby et al. 1992), the anti-human CD4 antibody, CAMPATH-9 (Gorman et al. 1991), the anti-human CD18 antibody 1B4, (Daugherty et al. 1991, Law et al. 1992), the anti-T cell receptor antibody BMA031 (Kurrle et al. 1990, Shearman et al. 1991b), the anti-HTLV-IIIb antibody, 0.5 $\beta$ (Maeda et al. 1991), the anti-human EGF receptor antibody, 425 (Kettleborough et al. 1991), and the anti-$p185^{HER2}$ antibody, 4D5 (Carter et al. 1992b). ...
>
> During the humanization of the 1B4 (Daugherty el al. 1991, Law et al. 1991), 0.5 $\beta$ (Maeda et al. 1991), and

> CAMPATH-9 (Gorman et al. 1991) antibodies, initial attempts to use the NEWM heavy chain, as described for the CAMPATH-1 humanization (Riechmann et al. 1988a), had proven unsuccessful in reconstituting binding activity"; see (**D59**) at page 16, last paragraph and page 17, first two paragraphs. The reference list of (**D59**) on page 37 lists the Queen and Selick 1990 citation as WO90/07861, which is the application from which the contested Patent descended.

This passage from an objective scientist is highly interesting for several reasons.

First, Dr. Adair here describes the homology-based method of the contested Patent as an alternative procedure to the method of Dr. Winter which was described earlier in his article. Moreover, Dr. Adair never suggests that this alternative procedure could have been derived from the earlier work of Dr. Winter or others.

Secondly, the passage makes clear that in 1992, only 2 years after publication of the patent application from which the contested Patent derives, the homology-based method was being widely used by many scientists. This rapid, widespread adoption of the method by the scientific community provides conclusive proof of its usefulness.

Finally, Dr. Adair points out several examples where the earlier method of Dr. Winter – which always utilized the NEWM heavy chain as acceptor – was unsuccessful in humanizing an antibody, while the homology-based method of the contested Patent was successful. For example, in Maeda (**D60**) cited by Dr. Adair, several different versions of a NEWM-based humanized heavy chain were made; see (**D60**), Fig. 2A on page 126 and the second paragraph under Results on page 129. However, none of these showed any binding to the antigen; see (**D60**) at page 130, first paragraph. In striking contrast, when a homology-based acceptor was used for the heavy chain, the humanized antibody had affinity within about 2-fold of the donor mouse antibody; see (**D60**) at page 130, second paragraph and page 131, first two paragraphs.

The Gorman (**D52**) paper, which was also cited by Dr. Adair, reports similar results. In fact, the principal observation of the Gorman (**D52**) article, which may have justified its publication in the prestigious journal *Proc. Natl. Acad. Sci. USA*, was that the homology-based method was highly successful for humanizing an anti-CD4 antibody, whereas the NEW-based method was not. This finding is highlighted in the abstract, introduction, results and discussion sections of Gorman (**D52**), for example:

> "We have made two reshaped antibodies that differ only in their usage of human $V_H$ region framework sequences, KOL and NEW, and found one form to be far superior to the other.... In this case then, it would seem that the selection of a human V region framework that was highly homologous to the rodent V region was the best strategy for framework selection. We have also successfully reshaped a CD3 antibody by the same approach (E.G.R., unpublished data), so this strategy may prove to be generally applicable to antibody reshaping"; see (**D52**) at page 4184, bottom of first column through first paragraph of second column (emphasis added).

This preference for the homology-based method of the contested Patent is especially noteworthy because Dr. Waldmann, the senior author of Gorman (**D52**), had earlier been a collaborator of Dr. Winter and a co-author of Riechmann (**D3**).

## 9.7 Summary

As has been demonstrated above, none of the cited documents teaches or suggests to consider the level of homology between the frameworks of the donor antibody and the acceptor antibody when humanizing antibodies. Thus, the claimed method of the present invention was not obvious to the person skilled in the art. Furthermore, as confirmed by post published art, the claimed method has been acknowledged as providing a general approach towards the successful humanization of antibodies. Accordingly, the claimed method solves the problem of providing a method for producing

humanized antibodies that enhances the chances of retaining antigen affinity.

Therefore, the method of claims 1 to 5 involve inventive step.

## 10. CONCLUSION

For the forgoing reasons, our request that the oppositions be rejected and the contested Patent be maintained on the basis of the enclosed new Main Request is fully justified.

Dr. Hans Rainer Jaenichen
European Patent Attorney

**Encl.:**
11 copies of a new main request
8 copies of the observations for the Opponents
9 copies of a list of cited documents (Annex I)
9 copies of documents D50 to D61
Authorization